for the required fee of $460.00, is submitted herewith, making the response due on January 29, 2003. Applicants respectfully request reconsideration and withdrawal of the rejections in view of the following amendments and remarks.

A version of the amended paragraphs of the specification is attached hereto as Appendix A, and a version of the amended claims is attached hereto as Appendix B, with the changes made by the present amendment indicated in bold.

AMENDMENTS

Amendments to the Specification

Please replace the paragraph at page 1, lines 5-7 of the specification with the following paragraph:

B1

This application is a §371 national phase application from International Application No. PCT/US98/13007, filed June 22, 1998, which is a continuation-in-part application of U.S. Application Serial No. 08/879,565, filed June 20, 1997, now U.S. Patent No. 6,093,573, which is hereby incorporated by reference in its entirety.

Please replace the paragraphs at page 14, lines 7-30, and page 15, lines 1-28 with the following paragraphs:

B2

Fig. 1A A ribbon diagram of residues 1-456 of BPI illustrating its boomerang shape. The NH_2-terminal domain is shown; the COOH-terminal domain and the two phosphatidylcholine molecules are shown. The linker is also shown, and the disulfide bond is shown as a ball-and-stick model. **Fig. 1B** View after rotating Fig. 1A 70° about the long axis of the molecule. Figure produced with MOLSCRIPT [P. Krauliz, *J. Appl. Cryst.*, *24*:926 (1991)] and RASTER3D [E. A. Merrit and M. E. P. Murphy, *Acta Crystallogr.*, *D50*:889 (1994); D. J. Bacon and W. F. Anderson, *J. Mo. Graphics*, *6*:219 (1988)].

Fig. 2A Schematic drawing of the novel BPI domain fold, shown in same orientation as the NH_2-terminal domain in Fig. 1B. **Fig. 2B** Superposition of the NH_2- and COOH-terminal domains of BPI showing the overall topological

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similarity. Residues 1 to 230 and 250 to 456 are shown. The NH_2-terminal domain is in the same orientation as Fig. 1A.

Fig. 3 Electron density of the final 2.8 Å MIR map contoured at 1.0 σ and superimposed on the refined model. The area shown is in the lipid binding pocket of the NH_2-terminal domain of BPI. The phosphatidylcholine and the surrounding protein atoms are shown.

Fig. 4A The covalent structure of phosphatidylcholine and the lipid A region of LPS from *E. coli and S. typhimurium*. Phosphate groups are indicated by P. Adapted with changes from [C. R. H. Raetz, *Annu. Rev. Biochem, 59*:129 (1990)]. **Fig. 4B** Slice through the interior of BPI showing the lipid binding pocket in the NH_2-terminal domain. The solvent accessible surface of the protein was calculated without lipid present, the interior of the protein and the phosphatidylcholine are shown. Protein residues are shown as ball-and-stick. Figure produced with MSP [M. L. Connolly, *Science, 221*:709 (1983); M. L. Connolly, *J. Am. Chem. Soc., 107*:1118 (1985)].

B2 Cont'd

B3

Figs. 5A and **5B** The amino acid sequences of human BPI (SEQ ID NO: 3), LBP (SEQ ID NO: 4), PLTP (SEQ ID NO: 5), and CETP (SEQ ID NO: 6). The alignment was performed with CLUSTAL [D. G. Higgins and P. M. Sharp, Gene, 73:237 (1989)] using all eleven known protein sequences from mammals [R. R. Schuman, et al., Science, 249:1429 (1990); D. Drayna et al., Nature, 327:632 (1987); R. Day et al., J. Biol. Chem., 269:9388 (1994); S. R. Leong and T. Camerato, Nucleic Acids Res., 18:3052 (1990); M. Nagashima, J. W. McLean, R. M. Lawn, J. Lipid Res., 29:1643 (1988); M. E. Pape, E. F. Rehber, K. R. Marotti, G. W. Melchior, Artheriosclerosis 11:1759 (1991); G. Su et al., J. Immunol., 153:743 (1994); P. W. Gray et al., J. Biol. Chem. 264: 9505 (1989); Albers et al., Biochem. Biophys. Acta, 1258:27 (1995); X. C. Jiang et al., Biochemistry, 34:7258 (1995); L. B. Agellon et al., Biochemistry, 29:1372 (1990); X. C. Jiang et al., J. Biol. Chem., 266:4631 (1991)] but only the four human sequences are shown. Residues that are completely conserved in all proteins are indicated below the sequence *; those which are highly conserved are indicated by •. The secondary structure of BPI is indicated above the sequences. The β strands are indicated by arrows; strands which make up the central β sheet are shown with gray arrows. Because of the β bulges and pronounced twisting, some of the β strands have one or more residues that do not show classical H-bonding patterns or ΦΨ angles; these

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breaks are indicated by ^ above the strands. The α helices are shown as cylinders, and one-residue breaks in helices B and B' are indicated with a vertical dashed line. The horizontal dashed line indicates the linker region. Peptides from BPI and LBP with the highest lipopolysaccharide-binding activity (Little, et al., J. Biol. Chem. 268: 1865 (1994); Taylor et al., J. Biol. Chem. 270: 17934 (1995)) are in bold italics. The disulfide bond is indicated by S-S. Residues with atoms within 4 Å of the NH_2 -terminal lipid are highlighted with gray shading; residues within 4 Å of the COOH-terminal lipid are shown with white letters in black boxes.

B3 Cont'd

Please replace the paragraph at page 43, line 27 to page 44, line 6 with the following paragraph:

B4

To allow insertion of BPI into an optimized mammalian expression vector, a unique *Xho*I site was first added to the 3′ end of the BPI gene in pIC108. Two oligonucleotides were synthesized for this purpose: BPI-53 (5′ ACT GGT TCC ATG GAG GTC AGC GCC 3′) (SEQ ID NO: 7) encoding amino acids 361 - 370 of BPI and BPI-54 (5′ GAC AGA TCT CTC GAG TCA TTT ATA GAC AA 3′) (SEQ ID NO: 8) encoding the last four amino acids of coding sequence, the stop codon (TGA), and incorporating an *Xho*I site immediately downstream of the stop codon. These oligonucleotides were used to PCR amplify a 280 bp fragment of the C-terminus of BPI and incorporate the *Xho*I site at the 3′ end of the gene. The amplified fragment was digested with *Nco*I and *Bgl*II and ligated to a ~4100 bp *Nco*I-*Bam*HI fragment from pIC108 to generate the plasmid pSS101.

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